

# World Journal of *Clinical Cases*

*World J Clin Cases* 2021 November 16; 9(32): 9699-10051



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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Jia-Hui Li; Production Department Director: Yu-Jie Ma; Editorial Office Director: Jin-Lai Wang.

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Thrice Monthly

**EDITORS-IN-CHIEF**

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

November 16, 2021

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<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Prospective Study

# Efficacy of Yiqi Jianpi anti-cancer prescription combined with chemotherapy in patients with colorectal cancer after operation

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**Institutional review board**

**statement:** The study was reviewed and approved by the institutional review board of Liaoning Cancer Hospital and Institute.

**Clinical trial registration statement:**

This study is not registered.

**Informed consent statement:**

All study participants, or their legal guardian, provided written consent prior to study enrollment.

**Conflict-of-interest statement:**

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## Abstract

### BACKGROUND

At present, colorectal cancer is routinely treated with adjuvant radiotherapy and chemotherapy postoperatively. The adverse effects (AEs) of chemotherapy usually interrupt the treatment of chemotherapy. Traditional Chinese medicine (TCM) has demonstrated great potential in improving patients' clinical symptoms, regulating the immune function, improving the life quality, and reducing the AEs of chemotherapy.

### AIM

To observe the clinical efficacy of Yiqi Jianpi anti-cancer prescription combined with chemotherapy in patients with colorectal cancer after operation.

### METHODS

Data from patients diagnosed with colorectal cancer between January 2019 and February 2021 were collected from Liaoning Cancer Hospital and Institute and the Second Affiliated Hospital of Liaoning University of Traditional Chinese Medicine. Patients receiving the chemotherapy regimen of capecitabine plus oxaliplatin (CAPOX) after radical resection of colorectal cancer were prospectively collected and randomly divided into an experimental group and a control group. The experimental group was given Yiqi Jianpi anti-cancer prescription combined with the CAPOX regimen, while the control group was given the CAPOX regimen alone. After six cycles of chemotherapy, the scores of TCM symptoms, Karnofsky performance scale (KPS) score, levels of T-cell subsets, and AEs after chemo-

There is no conflict of interest to disclose.

**Data sharing statement:** There is no additional data available.

**CONSORT 2010 statement:** The manuscript was checked and revised according to the CONSORT 2010 statement.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Specialty type:** Oncology

**Country/Territory of origin:** China

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): B, B  
Grade C (Good): 0  
Grade D (Fair): 0  
Grade E (Poor): 0

**Received:** June 22, 2021

**Peer-review started:** June 22, 2021

**First decision:** July 5, 2021

**Revised:** July 16, 2021

**Accepted:** August 25, 2021

**Article in press:** August 25, 2021

**Published online:** November 16, 2021

**P-Reviewer:** Kalofonos HP, Shinozaki E

**S-Editor:** Wang JL

**L-Editor:** Wang TQ

**P-Editor:** Wang LYT



therapy of the two groups were compared.

## RESULTS

A total of 70 patients were randomly divided into either an experimental group ( $n = 35$ , no dropout) or a control group ( $n = 33$ , with 2 dropouts). Compared with the control group, the experimental group improved significantly ( $P < 0.05$ ) in scores of TCM symptoms, KPS score, levels of T-cell subsets, and AEs of chemotherapy.

## CONCLUSION

Yiqi Jianpi anti-cancer prescription can effectively improve spleen deficiency, regulate the immune function, and alleviate the AEs of chemotherapy, so as to improve the life quality of patients with good therapeutic effects and application prospect in clinical practice.

**Key Words:** Yiqi Jianpi; Anti-cancer; Postoperative colorectal cancer; Immune function; Life quality; Chemotherapy; Adverse effects

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**Core Tip:** In this study, the authors found that the Yiqi Jianpi anti-cancer prescription can effectively improve spleen deficiency, regulate the immune function, and alleviate the adverse effects (hand-foot skin reaction and gastrointestinal reaction) of chemotherapy, so as to improve the life quality of patients with good therapeutic effects and application prospect in clinical practice.

**Citation:** Li Z, Yin DF, Wang W, Zhang XW, Zhou LJ, Yang J. Efficacy of Yiqi Jianpi anti-cancer prescription combined with chemotherapy in patients with colorectal cancer after operation. *World J Clin Cases* 2021; 9(32): 9869-9877

**URL:** <https://www.wjgnet.com/2307-8960/full/v9/i32/9869.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v9.i32.9869>

## INTRODUCTION

The incidence of gastrointestinal (GI) cancers has been rising in recent years, among which colorectal cancer is the most common one in clinical practice. Colorectal cancer is confirmed in 1.4 million new cases and 694000 deaths worldwide every year, making it the third largest malignant tumor[1]. At present, colorectal cancer (stages I-III) is mainly treated by radical resection; however, recurrence and metastasis remain the most common causes of death from it[2]. Accordingly, colorectal cancer is routinely treated with adjuvant radiotherapy and chemotherapy postoperatively. Clinical studies have demonstrated that surgery and chemotherapy could damage the immune function and influence the life quality of the patients. In addition, the adverse effects (AEs) of chemotherapy usually interrupt the treatment of chemotherapy as well. Traditional Chinese medicine (TCM) has demonstrated great potential in improving patients' clinical symptoms, regulating the immune function, improving the life quality, and reducing the AEs of chemotherapy[3]. This controlled clinical study evaluated patients with colorectal cancer after operation treated with Yiqi Jianpi anti-cancer prescription and chemotherapy between January 2019 and February 2021.

## MATERIALS AND METHODS

### General information

This study was a multicenter, prospective, randomized, controlled study. Data from patients diagnosed with colorectal cancer between January 2019 and February 2021 were collected from two hospitals, the Liaoning Cancer Hospital & Institute and the Second Affiliated Hospital of Liaoning University of Traditional Chinese Medicine. The hospitalized patients receiving the chemotherapy regimen of capecitabine plus oxaliplatin (CAPOX) after radical resection were included. According to the order of

hospitalization and random numbers generated by computer, a total of 70 patients were randomly divided into two groups: Experimental group ( $n = 35$ , no dropout) and control group ( $n = 33$ , with 2 dropouts). There were 21 males and 14 females in the experimental group, and 22 males and 11 females in the control group. Before the treatment, the routine blood parameters, liver and kidney function, levels of ions, clotting function, electrocardiogram (ECG), and other indicators were all normal, with no contraindications to chemotherapy. Further, there were no significant differences in gender, age, cancer type, or scores of TCM symptoms between the two groups ( $P > 0.05$ ), as shown in [Table 1](#).

### Subjects

According to the Internal Medicine of Chinese Medicine (9<sup>th</sup> edition)[5], the diagnostic criteria for spleen deficiency include poor appetite, abdominal distention after eating, loose stool, tired body, lack of breath, disinclination to talk, fatigue, emaciation, and swelling limbs. Meanwhile, the lingual channel presents with pale tongue and teeth prints, white tongue coating, and weak pulse.

Patients were included according to the inclusion criteria: (1) Patients with colorectal cancer confirmed by surgical pathology and receiving the chemotherapy regimen of CAPOX for the first time; colorectal cancer was diagnosed according to the criteria in Standards for the Diagnosis and Treatment of Common Malignant Tumors [4] compiled by the Department of Medical Administration of the People's Republic of China; (2) Karnofsky performance scale (KPS) score  $> 70$ ; (3) Routine blood parameters, liver and renal function, ion levels, coagulation function, ECG, and other indicators were all normal, with no contraindications to chemotherapy; (4) 24–70 years old; (5) Two researchers (associate chief physician or above) both diagnosed the patient as having spleen deficiency; and (6) Patients with good compliance, who accepted the treatments and signed an informed consent form.

Patients were excluded according to the exclusion criteria: (1) Patients with serious complications of the heart, brain, or kidney; (2) Recent participation in other clinical trials; (3) Patients with severe and uncontrolled pathological changes or infections in organs, who cannot tolerate chemotherapy; (4) Patients with brain metastasis of colorectal cancer; and (5) Patients receiving other TCM anti-tumor drugs.

Patient dropout, withdrawal, and termination were determined according to the following criteria: (1) Patients with poor compliance, unable to cooperate with the researchers during the treatment period; (2) Patients with severe drug allergy during the treatments; (3) Patients with sudden and dramatic progression in the disease, requiring changes in chemotherapy regimens; (4) Patients who withdrew during the study voluntarily due to drug intolerance or personal reasons; and (5) Patients with previous injury or desquamation on hands and feet, which may influence the results of this study.

Patients and their family members were fully informed of the objectives of the study, and provided informed consent before the start of the treatments. This study was reviewed and approved by the Ethics Committees of Liaoning Cancer Hospital & Institute and the Second Affiliated Hospital of Liaoning University of TCM.

### Groups and treatments

Patients were divided into either an experimental or a control group. In the experimental group, the patients received the chemotherapy regimen of CAPOX consisting of oxaliplatin ( $130 \text{ mg/m}^2$ ) administered on day 1 and capecitabine ( $1000 \text{ mg/m}^2$ ) administered on days 1–14. Yiqi Jianpi anti-cancer prescription was combined with chemotherapy. A 21-d cycle for a maximum of six cycles was administered to the patients. Yiqi Jianpi anti-cancer prescription consisted of *Radix pseudostellariae*, *Poria*, *Atractylodes*, licorice root, *Amomum villosum* Lour., pinellia, *Iphigenia*, Tuckahoe, Zhejiang, *Fritillaria*, *Hedyotis diffusa* WILLD, coix seed, *Curcuma phaeocaulis* Valetton, and barbed skullcap herb. In the control group, the patients received the chemotherapy regimen of CAPOX only.

### Observation of clinical effects

Indicators of clinical effects included scores of TCM symptoms, KPS score, levels of T-cell subsets, and AEs scores. The indicators were assessed and recorded before and after the treatments (within 1 mo). For scores of TCM symptoms, the symptoms, signs, tongue, and channel of the patients were observed and recorded according to the Guidelines for Clinical Research of New Chinese Medicine[6]. The TCM symptoms of spleen deficiency for the patients receiving chemotherapy regimen of CAPOX after radical resection of colorectal cancer mainly included five items: Poor appetite,

**Table 1 Comparison of general information of the patients between the two groups**

Group	n	Gender(n)		Age (yr)			Colorectal cancer	
		Male	Female	Max	Min	mean ± SD	Colon cancer	Rectal cancer
Experimental	35	21	14	67	40	52.24 ± 13.20	28	7
Control	33	22	11	68	42	55.63 ± 12.39	25	8

abdominal distension, loose stool, fatigue, and emaciation. Each symptom was scored 0, 1, 2, or 3 points for none, mild, moderate, and severe manifestations in clinical practice, respectively. Regarding KPS score, 0–100 points were assigned to the patients according to the symptoms of the patients. The levels of CD3+, CD4+, and CD8+ T-cell subsets were detected by flow cytometry, and CD4+/CD8+ ratio was calculated. AEs of chemotherapy included rashes, hand-foot skin reaction (HFSR), and GI reactions based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0, as shown in Tables 2 and 3. Safety indicators included blood routine tests, liver and kidney function, coagulation function, and ECG.

### Statistical analysis

Data analyses were performed using SPSS 22.0. Categorical variables are described as absolute numbers and proportions. For continuous variables, the normality test was performed, and those with a normal distribution are presented as the mean ± SD. The differences of the distribution of the disordered and ordered categorical variables were compared using Pearson  $\chi^2$  and Wilcoxon tests, respectively. The continuous variables were compared using Student's *t*-test. A two-sided *P* value < 0.05 was considered statistically significant.

## RESULTS

### Comparison of scores of TCM symptoms between the two groups

After the treatments, the scores of TCM symptoms in the experimental group were significantly lower than those in the control group, as shown in Table 4.

### Comparison of KPS scores between the two groups

After the treatments, the KPS scores of both the experimental and control groups were significantly higher than those before the treatments (*P* < 0.05). Before the treatments, there was no significant difference in KPS scores between the two groups (*P* > 0.05). After the treatments, the KPS score of the experimental group was significantly higher than that of the control group (*P* < 0.05), as shown in Table 5.

### Comparison of serum levels of T-cell subsets between groups before and after the treatments

Before the treatments, no significant differences in serum levels of T-cell subsets were observed between groups (*P* > 0.05). After the treatments, the serum levels of CD3+ and CD4+ T-cell subsets and CD4+/CD8+ ratio in both groups were significantly increased while the level of CD8+ T-cell subset was significantly lower when compared to those before the treatments. In addition, the serum levels of T-cell subsets before and after the treatments in the experimental group was significantly higher than those in the control group (*P* < 0.05), as shown in Table 6.

### AEs of chemotherapy

**Comparison of grades of nausea:** After the treatments, the distribution of the grades of nausea between the two groups was significant different, with lower grades in the experimental group (*Z* = -3.25, *P* < 0.05), as shown in Table 7.

**Comparison of grades of HFSR:** After the treatments, the distribution of the grades of HFSR between the two groups was significant different, with lower grades in the experimental group (*Z* = -4.527, *P* < 0.05), as shown in Table 8.

### Comparison of safety between the experimental and control groups

After the treatments, there were AEs of chemotherapy found among the patients in

**Table 2 Hand-foot skin reactions (National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0)**

Grade	Item description
0	No clinical manifestations
1	Have red or discolored skin or painless dermatitis
2	Show changes in skin (such as peeling, bleeding, and swollen) or have blisters or sores, without any dysfunction
3	Show changes in skin due to dysfunctions caused by ulcerative dermatitis or pain

**Table 3 Gastrointestinal reactions (National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0)**

Grade	Item description
0	No clinical manifestations
1	Lack of appetite, without any change in eating habits
2	Less food intake, no significant weight loss or malnutrition, have signs of intravenous fluid replacement for < 24 h
3	Less energy and water intake, have signs of intravenous fluid rehydration, tube feeding and parenteral nutrition ≥ 24 h

**Table 4 Comparisons of scores of traditional Chinese medicine symptoms between the two groups (mean ± SD points)**

Group	n	Poor appetite	Abdominal distention	Loose stool	Fatigue	Emaciation
Experimental	35	1.11 ± 0.760 <sup>a</sup>	1.40 ± 0.728 <sup>a</sup>	1.37 ± 0.209 <sup>a</sup>	1.37 ± 0.501 <sup>a</sup>	1.54 ± 0.625 <sup>a</sup>
Control	33	2.75 ± 0.741	2.21 ± 0.753	2.64 ± 0.521	2.24 ± 1.122	2.15 ± 0.917

<sup>a</sup>*P* < 0.05 vs control group.

**Table 5 Comparison of Karnofsky performance scale scores between the two groups (mean ± SD points)**

Group	n	Before the treatments	After the treatments
Experimental	35	79.17 ± 4.125	88.51 ± 6.773 <sup>a,d</sup>
Control	33	78.75 ± 3.475	81.44 ± 4.539 <sup>a</sup>

<sup>a</sup>*P* < 0.05 vs before treatment.

<sup>d</sup>*P* < 0.05 vs control group.

**Table 6 Comparison of serum levels of T-cell subsets between groups before and after the treatments (mean ± SD)**

Group	n	Time	CD3+ (%)	CD4+ (%)	CD4+/CD8 (%)	CD8+ (%)
Experimental	35	Before treatment	41.52 ± 5.21	32.07 ± 3.31	0.51 ± 0.15	52.25 ± 5.37
		After treatment	62.3 ± 5.53 <sup>a,d</sup>	43.4 ± 4.99 <sup>a,d</sup>	1.02 ± 0.29 <sup>a,d</sup>	40.52 ± 4.58 <sup>a,d</sup>
Control	33	Before treatment	42.52 ± 4.58	31.15 ± 3.25	0.55 ± 0.13	52.12 ± 6.59
		After treatment	53.25 ± 6.62 <sup>a</sup>	37.72 ± 4.56 <sup>a</sup>	0.77 ± 0.15 <sup>a</sup>	48.46 ± 5.58 <sup>a</sup>

<sup>a</sup>*P* < 0.05 vs before treatment.

<sup>d</sup>*P* < 0.05 vs control group.

both groups. The distribution of myelosuppression, liver dysfunction, and kidney dysfunction, coagulation disorder, and ECG abnormality in the experimental group was not significantly different from that of the control group (*P* > 0.05), as shown in Table 9.

Table 7 Comparison of grades of nausea between the two groups

Group	n	Grade			
		0	1	2	3
Experimental	35	12	15	7	1
Control	33	4	7	16	6

Table 8 Grades of hand-foot skin reactions between the two groups

Group	n	Grade			
		0	1	2	3
Experimental	35	10	13	11	1
Control	33	3	8	19	3

Table 9 Adverse effects between the two groups, n (%)

Group	n	Myelosuppression	Liver dysfunction	Renal dysfunction	Coagulation disorder	ECG abnormality
Experimental	35	8 (22.8)	7 (20.0)	1 (2.8)	3 (8.5)	3 (8.5)
Control	33	6 (18.1)	5 (15.1)	2 (6.0)	3 (9.1)	2 (6.1)

ECG: Electrocardiogram.

## DISCUSSION

As reported in Global Cancer Statistics 2018, the incidence of colorectal cancer ranks third (6.1%) and its mortality ranks second (9.1%) among all malignancies worldwide [7]. Colorectal cancer affects more than 1 million people worldwide every year [8]. With the changes in lifestyle and dietary habits among Chinese people, the incidence and mortality of colorectal cancer in China have also been increasing yearly. Among all malignant tumors, the incidence of colon cancer and rectal cancer ranked third and fifth, respectively, while their mortality ranked fourth and fifth, respectively [9]. Colorectal cancer is most likely to occur in the colon, rectum, and cecum. Radical surgery remains the main treatment for colorectal cancer [10]. However, studies have reported that 50% of patients might have local recurrence or metastasis within 2 years after surgery. Therefore, to improve its 5-year survival rate, postoperative adjuvant chemotherapy regimens, such as CAPOX or FOLFOX, were recommended to patients with colorectal cancer according to the guidelines of National Comprehensive Cancer Network and Chinese Society of Clinical Oncology (CSCO) [11]. CAPOX was recommended as first-line chemotherapy regimen for colorectal cancer after surgery in the CSCO guidelines in 2019, consisting of capecitabine plus oxaliplatin. Because of its convenience and high efficiency, oral administration of capecitabine has been commonly used in clinical practice. However, the patients with colorectal cancer presented body deficiencies. Radical surgery and postoperative adjuvant chemotherapy regimen of CAPOX would damage their normal immune function. In addition, HFSR and GI reactions may occur during chemotherapy, which would affect prognosis, overall survival, and quality of life of the patients [12]. Thus, this clinical problem needs to be solved with urgency.

In TCM, colorectal cancer is considered to belong to the category of "intestinal mass" or "loosening the bowels with blood." The earliest understanding of colorectal cancer among ancient physicians is found in *Lingshu (Spiritual Pivot)-five changes*, defining that "persons who are susceptible to diseases that accumulate in the intestine..." The *Full Book of Experience in Treating Sore and Ulcer* stated that "many people have irregular diet habits... do not defecate for a long time, finally leading to Yin-yang disharmony," attributing colorectal cancer to irregular diet habits and infection with external pathogens. In addition, *Shengji Zonglu - Shouliumen* stated that "qi-blood circulation runs not fluently ... Thus tumor occurs", which emphasized the function of qi-blood circulation in colorectal cancer. Duanmu *et al* [13] believed that colorectal cancer was

not caused by a single factor, but by the interaction of qi stagnation, blood stasis, and phlegm dampness, resulting in the accumulation of cancer poison in the intestine. Zheng *et al*[14] assumed that colorectal cancer was caused by deficiency of vital qi, spleen-kidney asthenia, chronic diarrhea, and damp toxin stagnation in the colon and rectum. In *TCM Treatment of Malignant Tumors* compiled by Gu *et al*[15], colorectal cancer was classified into five types, including internal accumulation of damp-heat, blood stasis and toxin stagnation, qi-blood deficiency, spleen-kidney Yang deficiency, and liver-kidney Yin deficiency. Statistical analysis by Wang *et al*[16] revealed that internal accumulation of damp-heat was the most common among patients experiencing non-surgical chemo-radiotherapy; qi-blood deficiency was the most common among patients after surgery; while spleen-kidney Yang deficiency was the most common among patients after chemotherapy. In modern society, scholars in Western medicine[17,18] believed that colorectal cancer first locates in the large intestine, and then progresses into the spleen, stomach, liver, and kidney with the development of the disease. As for TCM scholars, patients with cancers have body deficiencies and cancer evil is an endogenous factor. Among the patients with colorectal cancer, blood deficiency would become much more severe after surgery, combined with the AEs of chemotherapy in the spleen and stomach, making spleen deficiency the basic pathogenesis of colorectal cancer. Therefore, spleen-qi deficiency and qi-blood deficiency are its origin, while damp-heat, phlegm-turbidity, and blood stasis are its symptoms. In summary, colorectal cancer is deficient in origin and excessive in symptoms. Based on the pathogenesis of colorectal cancer, oral administration of Yiqi Jianpi anti-cancer prescription for patients with colorectal cancer was adopted in this study with the principles of nourishing qi, promoting the spleen, and eliminating pathogens.

In the prescription, *R. pseudostellariae*, Poria, and *Atractylodes* can nourish qi and promote the spleen, serving as monarch drugs; at the same time, Pinellia, and Villous Amomum Fruit may regulate qi and eliminate phlegm, serving as minister drugs. Considering that patients with cancers are usually characterized by deficiency in body, excess in symptoms, asthenia of healthy qi, and sthenia of pathogens, the combination of the Monarch and minister drugs would be beneficial to replenish but not stagnate qi. In addition, barbed skullcap herb, *C. phaeocaulis* Valetton, *H. diffusa* WILLD, Iphigenia, coix seed, Zhejiang-Fritillaria, and tuckahoe could clear heat, detoxify, soften hardness, dissipate mass, and dissolve dampness, serving as adjuvant drugs, so as to resist pathogens. Finally, licorice root served as the guide drug. In a word, using Yiqi Jianpi anti-cancer prescription in this study took both the body and the symptoms into account and invigorated qi, promoting the spleen, resolving phlegm, softening hardness, dissipating mass, clearing heat, and detoxifying.

In Yiqi Jianpi anti-cancer prescription, *R. pseudostellariae*, Poria, *Atractylodes*, licorice root, *A. villosum* Lour., and Pinellia have been proved to have obvious enhancing effects on immune functions, while barbed skullcap herb, *C. phaeocaulis* Valetton, *H. diffusa* WILLD, Iphigenia, coix seed, Zhejiang-Fritillaria, and tuckahoe could reduce the expression of Bcl-2 and Bax and regulate angiogenesis related molecules such as vascular endothelial growth factors and protein Kinase C, so as to induce the apoptosis of colorectal cancer cells, thereby improving the immune function of the body and inhibiting tumors[19]. Modern pharmacological studies have demonstrated the definite functions of Yiqi Jianpi anti-cancer prescription, including promoting tissue repair and regulating the immune function and intestinal flora[20]. The TCMs in Yiqi Jianpi anti-cancer prescriptions could significantly enhance the immunogenicity of tumor cells[21], improve the body's immune function, resist the immunosuppressive effect of chemotherapy, and clear free radicals. Furthermore, they could also directly inhibit tumor growth and promote the hematopoietic function of bone marrow, which are suppressed after chemotherapy. All the TCMs in the prescription combined not only supplement deficiency of qi and blood and invigorate spleen, but also eliminate pathogens. For patients with colorectal cancer after radical resection, the prescription was able to further kill tumor cells, inhibit tumor metastasis, reduce postoperative AEs of chemotherapy, and consolidate the clinical efficacy, which prolonged the overall survival and improved the quality of life of the patients.

Our study demonstrated that for postoperative colorectal cancer patients, Yiqi Jianpi anti-cancer prescription combined with the chemotherapy regimen of CAPOX could effectively improve the symptoms of spleen deficiency and immune function, reduce HFSR and GI reactions related with chemotherapy, and improve the quality of life of the patients. Based on these clinical effects, Yiqi Jianpi anti-cancer prescription can be further used in clinical practice. However, its mechanism remains unclear and should be further studied.

## CONCLUSION

Yiqi Jianpi anti-cancer prescription can effectively improve spleen deficiency, regulate the immune functions, and alleviate the AEs (HFSR and GI reaction) of chemotherapy, so as to improve the life quality of patients with good therapeutic effects and application prospect in clinical practice.

## ARTICLE HIGHLIGHTS

### Research background

The incidence of colorectal cancer is on the rise. The immune function of patients with colorectal cancer after adjuvant chemoradiotherapy affects their quality of life.

### Research motivation

Traditional Chinese medicine (TCM) has demonstrated great potential in improving patients' clinical symptoms, regulating the immune function, improving the life quality, and reducing the adverse effects (AEs) of chemotherapy.

### Research objectives

This study aimed to observe the clinical efficacy of Yiqi Jianpi anti-cancer prescription combined with chemotherapy in patients with colorectal cancer after operation.

### Research methods

The scores of TCM symptoms, Karnofsky performance scale (KPS) score, levels of T-cell subsets, and AEs after chemotherapy of the two groups were observed.

### Research results

Compared with the control group, the experimental group improved significantly in scores of TCM symptoms, KPS score, levels of T-cell subsets, and AEs of chemotherapy.

### Research conclusions

Yiqi Jianpi anti-cancer prescription can effectively improve spleen deficiency, regulate the immune function, alleviate the AEs of chemotherapy, and improve the life quality of patients with good therapeutic effects and application prospect in clinical practice.

### Research perspectives

Yiqi Jianpi anti-cancer prescription can be further used in clinical practice. It can invigorate qi, promote the spleen, dissipate mass, and detoxify. It can also improve spleen deficiency and the life quality of patients.

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